"Fibrinogen concentration significantly decreases after on-pump versus off-pump coronary artery bypass surgery: a systematic point-of-care ROTEM analysis"

Momeni, Mona ; Carlier, Cécile ; Baele, Philippe ; Watremez, Christine ; Van Dyck, Michel ; Matta, Amine ; Kahn, David ; Rennotte, Marie-Thérèse ; Glineur, David ; de Kerchove, Laurent ; Jacquet, Luc-Marie ; Thiry, Dominique ; Gregoire, André ; Eeckhoudt, Stéphane ; Hermans, Cédric

Abstract

OBJECTIVES: Studies have emphasized the importance of normal fibrinogen concentrations in surgical patients. The primary hypothesis of this study was that fibrinogen levels significantly decrease in on-pump coronary artery bypass graft (CABG) surgery versus off-pump coronary artery bypass graft (OPCAB) surgery. The second objective was to show that ROTEM (TEM International, GmbH, Munich, Germany) rapidly detects these abnormalities compared with standard tests. DESIGN: A prospective, nonrandomized study. SETTING: A university hospital. PARTICIPANTS: Forty-two and 62 patients in the CABG and OPCAB groups, respectively, undergoing first-time bypass surgery were included. INTERVENTIONS: CABG versus OPCAB surgery. MEASUREMENTS AND MAIN RESULTS: Routine coagulation tests and ROTEM values were measured before anesthesia (T0), after the first dose of heparin (T1), after protamine (T2), upon intensive care unit arrival (T3), and 4 hours postoperatively (T4). The outcome measures were followe...

Document type : *Article de périodique (Journal article)*

Référence bibliographique

Momeni, Mona ; Carlier, Cécile ; Baele, Philippe ; Watremez, Christine ; Van Dyck, Michel ; et. al. *Fibrinogen concentration significantly decreases after on-pump versus off-pump coronary artery bypass surgery: a systematic point-of-care ROTEM analysis.* In: *Journal of Cardiothoracic and Vascular Anesthesia*, Vol. 27, no. 1, p. 5-11 (2013)

DOI : 10.1053/j.jvca.2012.07.008

Fibrinogen Concentration Significantly Decreases After On-Pump Versus Off-Pump Coronary Artery Bypass Surgery: A Systematic Point-of-Care ROTEM Analysis

Mona Momeni, MD,* Cécile Carlier, MD,* Philippe Baele, MD,* Christine Watremez, MD, PhD,* Michel Van Dyck, MD,* Amine Matta, MD,* David Kahn, MD,* Marie-Thérèse Rennotte, MD,* David Glineur, MD, PhD,† Laurent de Kerchove, MD,† Luc-Marie Jacquet, MD, PhD,‡ Dominique Thiry, CCP,§ André Grégoire, CCP,§ Stéphane Eeckhoudt, PhD,‖ and Cédric Hermans, MD, PhD‖

Objectives: **Studies have emphasized the importance of normal fibrinogen concentrations in surgical patients. The primary hypothesis of this study was that fibrinogen levels significantly decrease in on-pump coronary artery bypass graft (CABG) surgery versus off-pump coronary artery bypass graft (OPCAB) surgery. The second objective was to show that ROTEM (TEM International, GmbH, Munich, Germany) rapidly detects these abnormalities compared with standard tests.**

Design: **A prospective, nonrandomized study.**

Setting: **A university hospital.**

Participants: **Forty-two and 62 patients in the CABG and OPCAB groups, respectively, undergoing first-time bypass surgery were included.**

Interventions: **CABG versus OPCAB surgery.**

Measurements and Main Results: **Routine coagulation tests and ROTEM values were measured before anesthesia (T0), after the first dose of heparin (T1), after protamine (T2), upon intensive care unit arrival (T3), and 4 hours postoperatively (T4). The outcome measures were followed until 4 hours postoperatively. Fibrinogen concentrations were significantly lower in the CABG versus the OPCAB group at T2 (170 ± 44 *v* 243 ± 73 mg/dL, $p < 0.001$) and T3 (179 ± 42 *v* 232 ± 68 mg/dL, $p < 0.001$). This was confirmed by significantly lower FIBTEM maximal clot firmness values at T2 (9 ± 4 *v* 14 ± 5 mm, $p < 0.001$) and T3 (9 ± 4 *v* 13 ± 6 mm, $p < 0.001$). In the CABG group, patients received significantly more transfusions of all blood products except fresh frozen plasma.**

Conclusions: **Fibrinogen concentration significantly decreases after cardiopulmonary bypass. ROTEM helps in its fast detection.**

KEY WORDS: fibrinogen, point-of-care test, ROTEM, cardiopulmonary bypass, coronary artery bypass graft surgery, thromboelastography

DESPITE MAJOR ADVANCES in cardiac surgery and cardiopulmonary bypass (CPB), patients undergoing cardiac surgery belong to the subgroup requiring most of the blood bank resources.[1] This is particularly the case in complex cardiac surgery. The transfusion rate in noncomplex cardiac surgery should be low. However, this depends on the incidence of preoperative anemia and dual antiplatelet therapy. Therefore, the fast detection of any coagulation abnormalities and proper treatment are necessary to limit perioperative bleeding and avoid unnecessary transfusion.

The European guidelines for the management of trauma patients recommend fibrinogen concentrations around 150 to 200 mg/dL.[2] However, increased bleeding has been observed in surgical patients with fibrinogen concentrations exceeding this latter threshold.[3,4] Furthermore, in bleeding cases in which crystalloids and colloids have been used to maintain normal blood volume, fibrinogen has been found to be the first coagulation factor to decrease to critically low values.[5] The authors prospectively studied a large group of patients undergoing first-time coronary artery bypass graft (CABG) surgery with or without CPB. The first aim of the study was to show that CPB significantly reduced plasma fibrinogen levels in the on-pump group (CABG) compared with the off-pump coronary artery bypass (OPCAB) group. The second objective was to show that the point-of-care whole-blood coagulation test ROTEM (TEM International, GmbH, Munich, Germany) can detect these abnormalities very soon compared with standard coagulation tests.

METHODS

This study was approved by La Commission d'Ethique Biomédicale Hospitalo-Facultaire de l'UCL, Brussels, Belgium (Belgian registration number: B40320085181; 2008/10DEC/350; Chairperson: Prof. J.M. Maloteaux) on December 10, 2008. The trial was registered with http://Clinicaltrials.gov (identifier: NCT 00825981). Written informed consent was obtained for each participating patient.

Patients older than 18 years undergoing CABG surgery with or without CPB between January 2009 and November 2009 were considered for the study. Exclusion criteria were the following: emergency surgery, redo

*From the Departments of *Anesthesiology, †Cardiac Surgery, ‡Cardiac Intensive Care Unit, §Perfusion Services, and ‖Hematology, Université Catholique de Louvain, Cliniques Universitaires Saint Luc, Brussels, Belgium.*

Address reprint requests to Mona Momeni, MD, Department of Anesthesiology, Cliniques Universitaires Saint Luc, Avenue Hippocrate 10/1821, 1200 Brussels, Belgium. E-mail: mona.momeni@uclouvain.be

1053-0770/2701-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2012.07.008

and/or combined surgery, a history of coagulation disorders, preoperative renal dysfunction (serum creatinine >2.0 mg/dL), or preoperative impaired liver function (aspartate and/or alanine aminotransferase > 30 U/L). Patients with a history of autoimmune disease and malignancy were excluded as well. Two senior surgeons familiar with both techniques were in charge of the surgery. The decision to perform on- or off-pump surgery was left to the discretion of the surgeon. Because OPCAB surgery has gained much interest and is the technique of choice in the authors' institution, there were more patients in the OPCAB group.

All the patients underwent median sternotomy. Patients in the CABG group underwent normothermic CPB at a standardized continuous nonpulsatile flow of 2.2 to 2.4 L/min/m^2. The CPB circuit was primed with 1,000 mL of Ringer's acetate solution (Plasmalyte; Baxter, SA Lessines, Belgium), 500 mL of hydroxyethyl starch solution (Voluven, Fresenius Kabi, Belgium), 5,000 U of heparin, and 0.5 g/kg of mannitol. Myocardial protection was achieved by the induction of electromechanical arrest with warm blood enriched with potassium chloride and magnesium sulfate. Heparinization aimed to maintain the kaolin-activated coagulation time (HR-ACT; Medtronic Inc, Minneapolis, MN) above 400 seconds before venous cannulation and during the whole CPB time. In patients undergoing OPCAB surgery, heparin was administered to obtain a perioperative ACT of >300 seconds. Subjects undergoing OPCAB surgery were kept warm by the intraoperative administration of warm fluids. Complete revascularization was achieved in both groups. After the completion of anastomoses, protamine sulfate (1,400 antiheparin IU/mL; Leo Pharma, Dublin, Ireland) was administered at a dose to achieve near preoperative ACT values.

Anesthesia was induced with midazolam, sufentanil, and propofol and continued with either propofol or sevoflurane. Muscle relaxation was achieved with rocuronium. All patients received cefamandole as antibiotic prophylaxis. In all patients, tranexamic acid was administered at a dose of 15 to 20 mg/kg before the incision. In patients undergoing surgery with CPB, the same dose was administered in the CPB prime. The intra- and postoperative intravascular volume replacement were left to the discretion of the physician in charge of the patient and were performed with crystalloids (Plasmalyte), hydroxyethyl starch solutions (Voluven at a maximal dose of 30 mL/kg) or gelatins (Gelofusine; Fresenius Kabi, Schelle, Belgium), and salvaged blood from cell saver devices. The red blood cell transfusion trigger was a hemoglobin concentration of 6.5 g/dL on CPB and 7.5 g/dL off bypass unless signs of poor tolerance developed. The transfusion of non–red blood cell components and fibrinogen concentrate was performed only if clinical bleeding (200 mL/h over 2 consecutive hours) was present in conjunction with abnormal point-of-care coagulation tests. Clinical bleeding also was diagnosed if the surgeons could not visualize clots in the surgical field after protamine injection.

Whole blood drawn from a radial artery was collected in tubes containing trisodium citrate and was sent to the laboratory via a pneumatic system for the routine laboratory tests. Fibrinogen was measured according to the Clauss system. Blood samples were obtained at 5 time points: before the induction of anesthesia (T0), after the first dose heparin injection (T1), 15 minutes after protamine injection (T2), upon intensive care unit (ICU) arrival (T3), and 4 hours postoperatively (T4). Blood samples for the blood cell count, routine coagulation analysis, and ROTEM were performed at each time point. At T0, blood also was drawn for an anti-Xa assay and point-of-care whole-blood impedance platelet aggregometry (Multiplate; Verum Diagnostica GmbH, Munich, Germany). For ROTEM, the authors investigated 2 activated tests: the EXTEM and the FIBTEM. They were performed with 300 μL of citrated blood and 20 μL of 0.2 mol/L calcium chloride with rabbit brain thromboplastin as an activator with the EXTEM test and cytochalasin D as an activator with the FIBTEM test. The ROTEM parameters measured included the coagulation time (CT), clot formation time (CFT), maximal clot firmness (MCF), and maximum of lysis (ML) for the EXTEM test and MCF for the FIBTEM test. The normal values were consistent with previously published data.[6] The tubes were brought manually to the blood bank where the ROTEM analysis was performed by specialized personnel. The physicians in charge of the patients were able to interpret the ROTEM results.

For the Multiplate test, the following agonists were used: the adenosine diphosphate (ADP) test, the arachidonic acid (ASPI) test, and the thrombin receptor-activating peptide (TRAP) test. To limit the number of blood analyses and because the authors focused on immediate postoperative coagulation abnormalities, all the patients were followed until 4 hours postoperatively, at which time the last laboratory tests were performed for the purposes of the study.

A previous observation of the patients undergoing CABG surgery with CPB revealed mean 4-hour postoperative fibrinogen concentrations of 200 ± 56 mg/dL (unpublished data). The primary goal was to show a fibrinogen difference of 50 mg/dL between the CABG and the OPCAB groups. For a power of 0.8 and an α of 0.05, 40 patients were required in each group. The authors decided to include at least 100 consecutive patients. All the data are expressed as mean ± standard deviation, median and interquartile range, or numbers and percentages as appropriate. Dichotomous parameters were analyzed using the Fisher exact test. All the variables were tested for normal distribution using the Kolmogorov-Smirnov test. A Student t test was used for data with a normal distribution. Continuous nonparametric data were analyzed with the Mann-Whitney U rank sum test with Bonferroni post hoc analysis. A Friedman analysis of variance test was used for nonparametric paired data with the time as the within factor and the group as the between factor. A linear regression analysis with the Pearson correlation coefficient was computed to analyze the correlation between continuous data. Statistical analysis was performed using Statistica (Data Analysis Software System, 2004) version 7 (StatSoft, Tulsa, OK). Statistical significance was accepted when p was <0.05. All p values were 2 tailed.

RESULTS

Figure 1 shows the study flow. A total of 104 patients were included, with 42 patients undergoing CABG surgery with CPB and 62 undergoing OPCAB surgery. Table 1 shows the preoperative demographic data. Table 2 displays the preoperative medications. Forty patients (95%) in the CABG group and 55 patients (89%) in the OPCAB arm took a daily dose of aspirin. Among these subjects, 25% and 16%, respectively, in the CABG and OPCAB groups had stopped their preoperative aspirin. The mean duration of the cessation was 6 days. Eight patients in the CABG group and 15 patients in the OPCAB group took a daily dose of 75 mg of clopidogrel, which was stopped in each of them at least 5 days preoperatively. According to the institutional guidelines, the last dose of low–molecular-weight heparin was injected the evening before the surgery. In the CABG group, the mean duration of the CPB time and the aortic cross-clamp time were 102 ± 35 and 73 ± 35 minutes, respectively. The mean volume used for the CPB (priming included) consisted of Voluven (832 ± 449 mL), Plasmalyte (828 ± 283 mL), and Gelofusine (186 ± 358 mL). There was no significant difference in the number of arterial grafts ($p = 0.53$) and venous grafts ($p = 0.13$) between both groups. The number of distal anastomoses was significantly higher in the CABG group ($p = 0.008$). The amount of cell saver was significantly higher in the CABG group. It should be noted that in all the patients undergoing cardiac surgery with CPB, the blood remaining in the bypass machine was salvaged at the end of the surgery and administered at the skin closure.

The results of perioperative coagulation tests are shown in Table 3. Patients in the CABG group showed significantly more

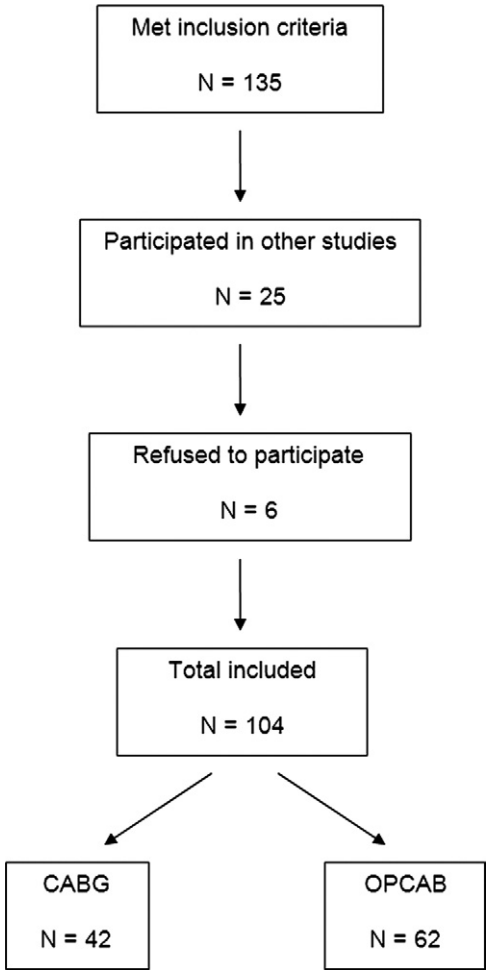

Fig 1. Study flow.

Table 2. Preoperative Medications

	CABG (n = 42)	OPCAB (n = 62)	*p* Value
Aspirin	40 (95)	55 (89)	0.52
Aspirin stopped preoperatively	10 (25)	8 (16)	0.29
Clopidogrel*	8 (19)	15 (24)	0.63
LMWH	11 (26)	22 (35)	0.39
Beta blocker	32 (76)	50 (81)	0.63
Ca antagonist	6 (14)	15 (24)	0.32
ACE inhibitor	26 (62)	40 (65)	0.84
Nitrate	17 (40)	22 (35)	0.68
Statin	33 (79)	48 (77)	0.99
Diuretics	9 (21)	15 (24)	0.82

NOTE. Data are expressed in numbers and percentages in brackets.
Abbreviation: LMWH, low–molecular-weight heparin.
*Clopidogrel was stopped in all the patients at least 5 days preoperatively.

disturbed coagulation tests after protamine injection and in the immediate postoperative period compared with the OPCAB group. This was confirmed by the EXTEM results shown in Table 4. The prolongation of the coagulation time in EXTEM reached statistical significance, and this prolongation resulted in a therapeutic intervention in case of ongoing bleeding. The main finding of this study was that among the routine coagulation tests, the plasma fibrinogen concentrations were significantly lower in the CABG group compared with the OPCAB group after protamine injection (ie, 170 ± 44 mg/dL; 95% confidence interval [CI], 156-184 *v* 243 ± 73 mg/dL; 95% CI, 223-262; $p < 0.001$) and upon ICU arrival (179 ± 42 mg/dL; 95% CI, 167-193 *v* 232 ± 68 mg/dL; 95% CI, 215-249; $p < 0.001$; Table 3). Concomitant with these results, the FIBTEM MCF values also were disturbed significantly in the CABG group versus the OPCAB group (Fig 2). After heparin reversal, the MCF values of the FIBTEM test in the CABG group were 9 ± 4 mm (95% CI, 8-11) versus 14 ± 5 mm (95% CI, 12-15) in the OPCAB group ($p < 0.001$). Upon ICU arrival, the CABG group showed FIBTEM-related MCF values of 9 ± 4 mm (95% CI, 7-10) versus 13 ± 6 mm (95% CI, 11-14) in the OPCAB arm ($p < 0.001$). The delta decrease in FIBTEM MCF values between T2 and T0 and between T3 and T0 were significantly higher in the CABG group compared with the OPCAB group ($p = 0.004$ and $p < 0.001$, respectively). Although the serum fibrinogen concentrations were above the

Table 1. Preoperative Characteristics of Patients

	CABG (n = 42)	OPCAB (n = 62)	*p* Value
Age (y), mean ± SD	66 ± 11	68 ± 11	0.35
Weight (kg), mean ± SD	79 ± 16	79 ± 15	0.99
Sex male	31 (73)	41 (66)	0.65
Hb (g/dL), mean ± SD	13.4 ± 1.7	12.9 ± 1.7	0.16
Creatinine (mg/dL), mean ± SD	1.08 ± 0.3	1.11 ± 0.37	0.65
Arterial hypertension	35 (83)	48 (77)	0.47
Hypercholesterolemia	33 (79)	52 (84)	0.61
Active smoking	9 (21)	14 (23)	0.99
Diabetes	10 (24)	18 (29)	0.65
Previous MI	14 (33)	24 (39)	0.68
Ejection fraction (%)	54 ± 13	55 ± 13	0.73
Log EuroSCORE, median (95% CI)	2.23 (1.7-4.09)	3.36 (2.32-4.81)	0.17

NOTE. Data are expressed as numbers and percentages in brackets unless otherwise stated.
Abbreviations: Hb, hemoglobin; MI, myocardial infarction; Log EuroSCORE, logistic EuroSCORE.

Table 3. Results of Coagulation, Multiplate, and Anti-Xa Tests at Several Time Points

	Baseline	Heparin Injection	Protamine Injection	ICU Arrival	4 h Postoperatively
Multiplate					
CABG					
AUC ADP	650 ± 290				
AUC ASPI	358 ± 260				
AUC TRAP	939 ± 267				
OPCAB					
AUC ADP	598 ± 303				
AUC ASPI	327 ± 297				
AUC TRAP	970 ± 343				
Anti-Xa					
CABG	0.06 ± 0.12				
OPCAB	0.08 ± 0.13				
Hb(g/dL)					
CABG	12.7 ± 1.7	11.2 ± 1.5*	8.6 ± 1.3*‡	10.3 ± 1.3*	10.0 ± 1.2*
OPCAB	12.1 ± 1.7	10.8 ± 1.6*	9.7 ± 1.5*	10.0 ± 1.4*	10.0 ± 2.1*
Platelet count (1,000/mL)					
CABG	227 ± 69	208 ± 58*	126 ± 51*	137 ± 36*†	136 ± 39*
OPCAB	212 ± 51	198 ± 49*	136 ± 46*	156 ± 45*	147 ± 41*
PT (s)					
CABG	11.3 ± 0.7	20.8 ± 5.7*‡	14.6 ± 1.3*†	12.8 ± 1.0*†	12.1 ± 0.6*†
OPCAB	11.1 ± 0.5	15.1 ± 1.6*	13.8 ± 1.1*	12.3 ± 0.7*	11.7 ± 0.8*
aPTT (s)					
CABG	26.3 ± 2.8	>180*	34.7 ± 6.6*†	35.9 ± 23.3*†	37.2 ± 12.3*†
OPCAB	25.6 ± 2.1	>180*	31.9 ± 3.7*	29.5 ± 3.6*	31.6 ± 5.8*
INR					
CABG	1.04 ± 0.05	1.99 ± 0.59*	1.37 ± 0.12*†	1.91 ± 0.09*†	1.22 ± 0.05*†
OPCAB	1.02 ± 0.05	1.41 ± 0.15*	1.29 ± 0.11*	1.15 ± 0.07*	1.08 ± 0.07*
Fibrinogen					
CABG	318 ± 69	265 ± 60*	170 ± 44*‡	179 ± 42*‡	198 ± 50*
OPCAB	357 ± 98	307 ± 83*	243 ± 73*	232 ± 68*	231 ± 81*

NOTE. Data are expressed as mean ± standard deviation.

Abbreviations: Hb, hemoglobin; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; AUC ADP, area under curve adenosine diphosphate test (normal range: 607-963); AUC ASPI, area under curve arachidonic acid test (normal range: 505-1,086); AUC TRAP, area under curve thrombin receptor-activating peptide, area under curve thrombin receptor activating peptide (normal range: 868-1,473).

*$p < 0.001$ within group.

†$p < 0.05$ between groups.

‡$p < 0.001$ between groups.

trigger values of 100 mg/dL, the authors administered human fibrinogen concentrate to stop bleeding in 5 patients in the CABG group (Table 5). This decision was based on the pathologic FIBTEM results. Two patients who received human fibrinogen concentrate also received fresh frozen plasma based on the pathologic ROTEM results. None of the patients in the OPCAB group required fibrinogen concentrate.

The CABG group showed significantly lower platelet numbers upon ICU arrival. This was confirmed again by the results of the EXTEM test, which were more pathologic in the CABG group. Significantly more patients in the CABG group also required transfusion of platelets based on the EXTEM results. The administration of blood products mainly was performed in the operating room. It should be noted that the results of the Multiplate realized at baseline did not show any significant differences between groups. In the CABG group, 48%, 74%, and 38% had abnormal ADP, ASPI, and TRAP test results, respectively. In the OPCAB arm, 48%, 77%, and 37% showed abnormal ADP, ASPI, and TRAP test results, respectively. There was no correlation between the baseline Multiplate tests and the transfusion requirements. The Multiplate test was only performed at baseline; therefore, the platelet function was not evaluated after CPB to predict the need for platelet transfusion. No correlation could be observed between the duration of CPB and the decrease in FIBTEM MCF values. The authors did not find any correlation between FIBTEM MCF values and the transfusion of blood products. Interestingly, immediate postoperative bleeding was not significantly different between the 2 groups as shown in Table 5. One patient in each group needed revision for bleeding. The bleeding was revealed to be of a surgical origin in both patients.

DISCUSSION

The main finding of this study was that compared with the OPCAB group, CPB significantly decreased plasma fibrinogen levels although other coagulation tests also showed some abnormalities. The decrease in plasma fibrinogen levels was significant after the protamine injection and upon

Table 4. EXTEM Values at Several Time Points

EXTEM Variable	Baseline	Heparin Injection	Protamine Injection	ICU Arrival	4 h Postoperatively
CT (s, normal range: 42-74)					
CABG	55 (50-61)	103 (86-129)†	78 (70-85)†	67 (60-80)†	69 (62-77)†
OPCAB	53 (47-59)	95 (80-113)†	73 (64-83)†	62 (55-70)†‡	60 (54-72)†‡
CFT (s, normal range: 46-148)					
CABG	74 (60-85)	97 (70-122)†	135 (104-188)†	123 (108-147)†	125 (101-151)†
OPCAB	64 (52-81)	74 (63-99)†‡	103 (74-127)†‡	96 (82-134)†‡	99 (78-135)†‡
MCF (mm, normal range: 49-71)					
CABG	63 (60-66)	61 (60-65)*	55 (49-60)†	55 (51-58)†	55 (52-59)†
OPCAB	64 (60-67)	64 (60-68)*	57 (54-62)†‡	58 (54-62)†‡	59 (54-63)†‡
ML (%, normal range: 0-15)					
CABG	16 (11-19)	9 (5-12)†	10 (7-14)†	10 (8-15)*	11 (8-15)*
OPCAB	14 (11-19)	11 (7-17)*‡	12 (8-16)*	11 (8-14)*	14 (10-17)

NOTE. Data are expressed as median (25th percentile-75th percentile).
Abbreviations: CT, coagulation time; CFT, clot formation time; MCF, maximal clot firmness; ML, maximum of lysis.
*$p < 0.05$ within group.
†$p < 0.001$ within group.
‡$p < 0.05$ between groups.

ICU arrival. The authors were able to treat hemostasis perturbations within 4 hours postoperatively. These observations agreed with previous studies in which fibrinogen was the first coagulation test to decline after major surgery.[5] This was mainly because of the hemodilution of CPB and blood loss.[7] The present findings also confirmed the widely accepted concept that CPB may result in impaired coagulation. The results of this study are in line with the available data showing the impact of OPCAB on transfusion requirements and/or postoperative bleeding.[8,9]

The decrease in coagulation parameters was confirmed by the EXTEM and FIBTEM tests. Interestingly, the low fibrinogen concentrations in the CABG group, which still exceeded the trigger value of 100 mg/dL, corresponded to the pathologic FIBTEM results. As expected, the EXTEM and FIBTEM results were both significantly more pathologic in the CABG group. It should be noted that the baseline fibrinogen levels of patients in the CABG group were lower than the OPCAB group although they were not significantly different ($p = 0.06$). Previous studies in cardiac surgery have shown an inverse relationship between preoperative plasma fibrinogen levels and postoperative bleeding.[3,10] This was not the case in the present study because the coagulation abnormalities were corrected very rapidly. By contrast, the delta decrease in FIBTEM compared with baseline was higher in the CABG group versus the OPCAB group. This shows that the relative decrease in fibrinogen concentrations might be an important factor as well.

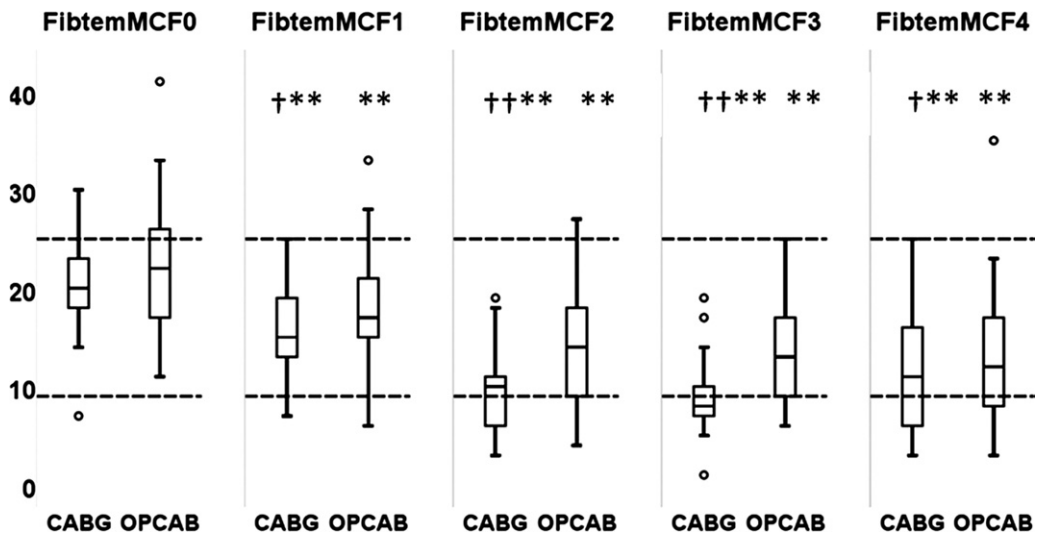

Fig 2. FIBTEM MCF results at several time points. Box and whisker plots of FIBTEM MCF values. The boxes represent the lower (25th) and upper (75th) quartiles, and the horizontal line represents the median. The whiskers extend to the 1.5 interquartile range. The outliers are plotted as a circle. Dashed lines indicate the normal range of FIBTEM MCF. FibtemMCF0, T0; FibtemMCF1, T1; FibtemMCF2, T2; FibtemMCF3, T3; FibtemMCF4, T4. **$p < 0.001$ within group. †$p < 0.05$ between groups. ††$p < 0.001$ between groups.

Table 5. Intra- and Postoperative Characteristics of Patients

	CABG (n = 42)	OPCAB (n = 62)	*p* Value
Number of patients transfused with packed RBC (%)	26 (62)	23 (37)	0.02
Number of patients transfused with platelets (%)	8 (19)	1 (2)	<0.001
Number of patients transfused with FFP (%)	7 (17)	3 (5)	0.09
Number of patients transfused with fibrinogen (%)	5 (12)	0	<0.001
Units packed RBC transfused, median (IQR)	3 (2,4)	2 (1,3)	0.02
Units platelets transfused, median (IQR)	12 (11,13)	0	<0.001
Units FFP transfused, median (IQR)	2 (2,3)	3 (2,3)	0.06
Intraoperative cell salvage, mL	728 ± 230	360 ± 374	<0.001
Voluven, mL			
Intraoperative (CPB volume excluded)	656 ± 465	1155 ± 442	<0.001
Postoperative	630 ± 429	533 ± 382	0.09
Gelofusin, mL			
Intraoperative (CPB volume excluded)	60 ± 198	48 ± 149	0.99
Postoperative	488 ± 374	510 ± 327	0.5
Plasmalyte, mL			
Intraoperative (CPB volume excluded)	785 ± 380	1146 ± 442	<0.001
Postoperative	0	0	
Number of revisions for bleeding	1	1	NS
Postoperative bleeding			
First hour, mL	86 ± 80	64 ± 68	0.08
Second hour, mL	92 ± 169	47 ± 32	0.06
Third hour, mL	64 ± 71	55 ± 50	0.26
Fourth hour, mL	58 ± 57	40 ± 32	0.08
Cumulative 4-h blood loss, mL	295 ± 286	204 ± 133	0.23

NOTE. Data are expressed as mean ± standard deviation unless otherwise stated.
Abbreviations: RBC, red blood cell; FFP, fresh frozen plasma; IQR, interquartile range; NS, not significant.

The second important observation of this study was that, based on the ROTEM results,[6] the authors were able to detect the coagulation abnormalities within 20 minutes and substitute the necessary coagulation factors. The FIBTEM results were particularly helpful in the decision to administer fibrinogen concentrate. Five bleeding patients in the CABG group received 1 g of lyophilized fibrinogen concentrate each, after which the bleeding was stopped. These results highlight the importance of high normal fibrinogen concentrations in the maintenance of normal hemostasis. Indeed, in recent years, much attention has been focused on the critical role of fibrinogen in the coagulation cascade.[11,12] Therefore, numerous studies in cardiac surgery have been conducted, aiming to prevent bleeding by transfusing high doses of fibrinogen concentrate.[13-15] However, the dose of fibrinogen concentrate administered in this study was much lower than that in the studies of Rahe-Meyer et al.[13,14] The present authors administered fibrinogen only if the FIBTEM MCF was <9 mm. This is in contrast to previous studies in which FIBTEM MCF values of 22 mm were targeted. In the latter studies, the authors aimed to reduce the use of fresh frozen plasma and platelet concentrates by targeting high FIBTEM MCF values.

An important point to be considered is that there was no significant difference in the postoperative bleeding of the groups during the first 4 hours after arrival in the ICU. The authors believe this was the result of fast and rational transfusion of the necessary coagulation factors. Although in several countries the use of blood products is predominant for cardiovascular surgery,[1] there is a wide variation regarding the blood conservation and transfusion policy in this field.[16] A rational hemostatic therapy guided by point-of-care testing seems mandatory in cardiac surgery. In a very recent retrospective study, the use of point-of-care testing was associated with a decreased incidence of blood transfusion and thrombotic/thromboembolic events.[17] Although the primary endpoint of the present study was not the incidence of intraoperative allogeneic blood transfusion and it was not designed to compare a ROTEM-guided transfusion group with a control group, the authors believe that unnecessary re-exploration and major postoperative bleeding were avoided by the fast administration of adequate coagulation factors. These results are in line with other studies showing the benefits of ROTEM-guided transfusion policy in the management of patients at high risk of transfusion.[18-21]

This was a nonrandomized prospective study. The main aim of this study was to underline the importance of fibrinogen levels in achieving hemostasis and, in particular, in surgery with CPB. However, no bias could be excluded because the decision in terms of type of surgery was only made by the surgeon. Another important point to consider is that the physicians in charge of the patients were not blinded to the ROTEM results. Hence, a prospective, randomized, double-blind study should be encouraged to further prove the superiority of ROTEM compared with traditional coagulation tests in cardiac surgery. The nonblinded aspect of this study was also the reason why the authors could not find a correlation between FIBTEM MCF results and the transfusion requirements because these values already were used to guide the therapy with fibrinogen concentrate. It would be

interesting to investigate whether there was a correlation between ROTEM values and blood loss before any correction with fibrinogen. It should be noted that the "classic" transfusion algorithm was not followed in 5 patients in the CABG group with respect to the administration of human fibrinogen concentrate because the serum fibrinogen concentrations were above the trigger value of 100 mg/dL. Finally, this study was stopped at 4 hours postoperatively. Therefore, the recovery of coagulation tests after 24 hours has not been investigated.

In summary, the results of this study showed the detrimental effects of CPB on the coagulation parameters and, in particular, the fibrinogen concentrations. Point-of-care tests are helpful in the early detection of these abnormalities. This will guide physicians in the administration of the required transfusion products.

REFERENCES

1. Cobain TJ, Vamvakas EC, Wells A, et al: A survey of the demographics of blood use. Transfus Med 17:1-15, 2007
2. Rossaint R, Bouillon B, Cerny V, et al: Task Force for Advanced Bleeding Care in Trauma: Management of bleeding following major trauma: An updated European guideline. Crit Care 14:R52, 2010
3. Blome M, Isgro F, Kiessling AH, et al: Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. Thromb Haemost 93:1101-1107, 2005
4. Karlsson M, Ternström L, Hyllner M, et al: Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Thromb Haemost 102:137-144, 2009
5. Hiippala ST, Myllylä GJ, Vahtera EM: Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 81:360-365, 1995
6. Lang T, Bauters A, Braun SL, et al: Multi-centre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis 16:301-310, 2005
7. Chandler WL: Effects of hemodilution, blood loss, and consumption on hemostatic factor levels during cardiopulmonary bypass. J Cardiothorac Vasc Anesth 19:459-467, 2005
8. Raja SG, Dreyfus GD: Impact of off-pump coronary artery bypass surgery on postoperative bleeding: Current best available evidence. J Cardiovasc Surg 21:35-41, 2006
9. Ascione R, Williams S, Lioyd CT, et al: Reduced postoperative blood loss and transfusion requirement after beating-heart coronary operations: A prospective randomized study. J Thorac Cardiovasc Surg 121:698-696, 2001
10. Karlsson M, Ternström L, Hyllner M, et al: Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: A prospective observational study. Transfusion 48: 2152-2158, 2008
11. Mosesson MW: Fibrinogen and fibrin structure and functions. J Thromb Haemost 3:1894-1904, 2005
12. Weisel JW, Nagaswami C, Vilaire G, et al: Examination of the platelet membrane glycoprotein IIb-IIIa complex and its interaction with fibrinogen and other ligands by electron microscopy. J Biol Chem 267:16637-16643, 1992
13. Rahe-Meyer N, Pichlmaier M, Haverich A, et al: Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: A pilot study. Br J Anaesth 102:785-792, 2009
14. Rahe-Meyer N, Solomon C, Winterhalter M, et al: Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. J Thorac Cardiovasc Surg 138:694-702, 2009
15. Solomon C, Pichlmaier U, Schoechl H, et al: Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. Br J Anaesth 104:555-562, 2010
16. Likosky DS, FitzGerald DC, Groom RC, et al: Effect of the perioperative blood transfusion and blood conservation in cardiac surgery clinical practice guidelines of the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists upon clinical practices. Anesth Analg 111:316-323, 2010
17. Görlinger K, Dirkmann D, Hanke AA, et al: First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: A retrospective, single-center cohort study. Anesthesiology 115:1179-1191, 2011
18. Ogawa S, Szalm F, Chen EP, et al: A comparative evaluation of rotation thromboelastometry and standard coagulation tests in hemodilution-induced coagulation changes after cardiac surgery. Transfusion 52:14-22, 2012
19. Spalding GJ, Hartrumpf M, Sierig T, et al: Cost reduction of perioperative coagulation management in cardiac surgery: Value of "bedside" thromboelastography (ROTEM). Eur J Cardiothorac Surg 31:1052-1057, 2007
20. Girdauskas E, Kempfert J, Kuntze T, et al: Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: A prospective, randomized trial. J Thorac Cardiovasc Surg 140:1117-1124, 2010
21. Theusinger OM, Spahn DR, Ganter MT: Transfusion in trauma: Why and how should we change our current practice? Curr Opin Anaesthesiol 22:305-312, 2009